REMARKS

Claims 14, 18, 19 and 21 are pending in this application. Claim 14 is independent and claims 18, 19 and 21 depend directly or indirectly from claim 14. By this amendment, claims 14 and 19 are amended. No new matter is added with the amendment. With the entry of this amendment, claims 14, 18, 19 and 21 remain pending and active.

I. Claim Rejections – 35 USC § 112

The Examiner rejects claims 14, 18, 19 and 21 under 35 USC § 112, first paragraph, as failing to comply with the written description requirement.

The Office Action states that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. According to the Examiner, claim 14 introduces new matter as the claim recites the limitation: "remains stable after one month after being prepared." The Examiner states that there is no support in the Specification for the underlined limitation. Applicants respectfully traverse this rejection.

In further response, applicants herewith amend claim 14 to recite that the pharmaceutical composition is "in the form of a tablet" and that a sample of the composition in solid form subjected to accelerated stability testing at 60 degrees centigrade "for one month remains stable." Applicants have removed "after one month after being prepared." Support for this amendment can be found in the specification in Example 19, paragraph [0069].

In view of this clarifying amendment, applicants respectfully request the Examiner to withdraw this rejection.

II. Claim Rejections – 35 USC § 103

The Examiner rejects claims 14, 18, 19 and 21 under 35 USC § 103(a) as being unpatentable over Pflaum (US 6740775) (hereinafter "Pflaum"), in view of Yoshioka (Stability of Drugs and Dosage forms; 2000, Springer, 268 pages; pp 116-117) ("Yoshioka"). The Examiner believes that Pflaum teaches the same polymorph ("form Lek") recited in applicants' claims and that the claimed compositions are the result of routine optimizations. Yoshioka is cited for teaching the the microcrystalline absorbs water in tablet formulations to decrease degradation. The Examiner concludes that in the absence of unexpected results, the invention would have been obvious. Applicants respectfully traverse this rejection.

Although applicants concede that the crystalline pravastatin recited in claim 14 is taught by Pflaum, applicants maintain that Pflaum's teachings with regard to compositions comprising that polymorph are completely generic. Pflaum teaches tablets, capsules, granules, suppositories and suspensions (column 5, lines 25 and 26). Pflaum also teaches liquid compositions, which should be according to Yoshioka, completely unstable irrespective how much microcrystalline cellulose is used, particularly if the amount of microcrystalline cellulose would be less than the amount of pravastatin. Pflaum provides no specific guidance as how to provide a stabilized pharmaceutical composition, *i.e.* a mixture of compound, let alone a tablet. Indeed, Pflaum does not even recognize the problem addressed by the present invention. Therefore, Pflaum does not suggest or teach a solution to that problem, *i.e.*, that specifically selecting microcrystalline cellulose would have any impact on the stability of the claimed polymorph. Also, Pflaum provides no hint as to what ratio of pravastatin and microcrystalline cellulose should be used in wet phase. Pflaum does not even recognize obtaining tablets by wet granulation. A person of skill in the art would not have been motivated to consult Yoshioka and then combine it with Pflaum to arrive at the instant invention, as Yokishoba is not directed to an amount of microcrystalline

cellulose during wet phase. Yoshioka provides no teaching of the ratio of pravastatin to microcrystalline cellulose. Also, it does not provide any teaching as to when or where to incorporate microcrystalline cellulose in the pharmaceutical composition (or tablet). Also, the Examiner's citation of Yoshioka presupposes the mechanism of instability, *i.e.* instability due to hydrolysis, which might not be the stability issue in the case of pravastatin, or at least not the only one.

In Table 2 of the instant specification, Examples 5 and 6 show that a ratio of microcrystalline cellulose to pravastatin higher than 1 causes pravastatin of "form Lek" to convert to form D. Applicants discovered this phenomenon. The cited art teaches and suggests nothing about how or why the ratio of microcrystalline cellulose to pravastatin affects the polymorphic form of pravastatin.

In addition, applicants discovered that tablets containing pravastatin and obtained by wet granulation can satisfy all requirements of a medicine, such as friability, strength, dissolution, which with other processes cannot be readily achieved. Therefore, the tablets of claim 14, comprising a polymorph form of pravastatin sodium and microcrystalline cellulose in a ratio of pravastatin sodium to microcrystalline cellulose greater than one, wherein the greater than one ratio of pravastatin sodium to microcrystalline cellulose occurs at least in a wet phase, provides tablets that have superior stability, but also are ready to be used as a medicine. Thus, although the Examiner may consider some of the claimed features to be "process" features, the product obtained by such process is new and has improved stability and general utility, which also renders it non-obvious over the prior art's generic disclosure of various formulations. Pflaum does not teach pravastatin formulation obtained by wet granulation, let alone a polymorph of pravastatin that is stable.

Applicants assert that the product by process of the claimed invention is, in fact, not the same product suggested by the prior art. The product of claim 14 has specific intrinsic characteristics which are the inevitable consequence of the process language "occurs at least in a wet phase" and "wherein the wet phase comprises alcohol and the ratio of pravastatin sodium to alcohol is greater than one." That is, the product has the

intrinsic characteristic wherein the microcrystalline cellulose is in intimate mixture with pravastatin, which can be obtained only by wet granulation. Granulation liquid presumably solubilizes particles of microcrystalline cellulose and pravastatin and connects them into granules. This results in microcrystalline cellulose being intimately mixed with pravastatin, about which the prior art is completely silent. Simple mixing, particularly when done without compressing, like in the making of capsules, does not achieve all requirements of a usable medicine. Thus, the claimed invention is not simply an old product with a new property, but is clearly a new specific product, particularly usable product with all requirements for a product to be approved and commercialized.

Applicants argue that, for reasons outlined above, the subject matter of claim 14 achieves results unexpected in view of Pflaum and Yoshioka either alone or in combination. In view of these comments, applicants respectfully request the Examiner to reconsider and withdraw the rejection over these references as such rejections apply to all the pending claims.

The Examiner also rejects claims 14, 18, 19 and 21 under 35 USC § 103(a) as being unpatentable over Keri et al (WO 01/43723), (hereinafter "Keri et al"), in view of Yoshioka (Stability of drugs and dosage forms; 2000, Springer, 268 pages; pp 116-117). The Examiner states that Keri teaches adding microcrystalline cellulose to the formulation but simply does not disclose the weight ratio and that the weight ratio is a matter of routine optimization. Applicants respectfully traverse this rejection.

Keri discloses even more different possible compositions than does Pflaum. It teaches oral, buccal, parenteral, ophthalmic, rectal and transdermal formulations. With regard to oral formulations, Keri discloses tablets, pills, capsules, troches, sachets, suspensions, powders, lozenges, elixirs and the like (page 12, lines 17 to 20). Again, it does not disclose wet granulation as a possible step for preparing tablets. Nor does Keri recognize the stability problem solved by the claimed invention. Rather, Keri's description of formulations is general and broad, without any hint as what is used, apart that specifically disclosed pravastatin forms can be formulated into a composition. A skilled person reading Keri is left, as in the case of Pflaum, completely without any

specific guidance as to how to formulate the claimed polymorphic form of pravastatin in a stable and fit-to-use tablet. With regard to Yoshioka, a final product covered by instant claims has microcrystalline cellulose and pravastatin sodium in intimate mixture. This feature cannot be deduced from Yoshioka. Also, the right ratio cannot be deduced from Yoshioka. Neither Keri nor Yoshioka recognize the problem being solved by the claimed invention, accordingly, they do not direct the skilled artisan to a solution to that problem.

The Examiner's characterization of the claimed features of the invention as the result of simple optimization is not well taken because it does not recognize the fact that the inventors were seeking a solution to a problem unique to the claimed polymorph when formulated with microcrystalline cellulose as a tablet. It also does not recognize the fact that the claimed product has intrinsic features (i.e., the solubilizing particles of microcrystalline cellulose and pravastatin and connecting them into granules to make an intimate mixture) that are the result of the process selected by the inventors from an enormous number of possible processes for preparing a tablet.

In view of these arguments, applicants respectfully request the Examiner to reconsider and withdraw the rejection of all the pending claims over Keri, Pflaum and Yoshioka.

III. Double Patenting

The Examiner has rejected claims 14, 18, 19 and 21 on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 7, 14, 18, 19, 25, 32, 33, and 39 of U.S. Patent No. 6680341 ("the '341 patent") in view of Pflaum (US 6740775), and Yoshioka (Stability of drugs and dosage forms; 2000, Springer, 268 pages; pp. 116-117). The Examiner's argument appears to be that the '341 patent teaches stabilized formulations of pravastatin and fillers that encompass all polymorphic forms of pravastatin. The Examiner admits that the '341 patent does not teach formulations with microcrystalline cellulose of a particular size and ratio, but relies upon the teachings of Pflaum and Yoshioka with regard to microcrystalline cellulose

along with what the Examiner considers to be routine optimizations. Applicants respectfully traverse this rejection.

The claims in the '341 patent over which claims 14, 18, 19 and 21 are rejected are directed to stabilized forms of pravastatin, however, the critical variable identified in the '341 patent pertains to pH. None of claims 1, 7, 14, 18, 19, 25, 32, 33 or 39 in the '341 patent direct the skilled artisan to the problem identified by the applicants with regard to microcrystalline cellulose and the recited polymorph. Thus, the '341 patent and the recited claims provide no more direction toward the claimed invention than does Pflaum. Accordingly, the Examiner's reliance upon Pflaum and Yoshioka does not cure this deficiency, for reasons set forth above, in connection with the obviousness rejection. Withdrawal of this obviousness- type double patenting rejection is therefore respectfully requested.

The Examiner has rejected claims 14, 18, 19 and 21 on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 12, 13 and 17 of U.S. Patent No. 6531507 ("the '507 patent") in view of Pflaum and Yoshioka (Stability of drugs and dosage forms; 2000, Springer, 268 pages; pp. 116-117). The Examiner explains that the '507 patent teaches pharmaceutical formulations of sodium pravastatin and fillers and encompasses all polymorphs of sodium pravastatin. Although the '507 patent does not expressly teach the filler to be microcrystalline cellulose of a particular particle size and ratio with the active, the Examiner states that the art teaches using microcrystalline cellulose in sodium pravastatin formulations and teaches microcrystalline cellulose within the instant particle size. The Examiner asserts that it would be obvious to use microcrystalline cellulose in the pravastatin formulations taught in the '507 patent because the art suggests doing so. The Examiner again believes the recited ingredient ratios are routine optimizations. Applicants respectfully traverse this rejection.

The '507 patent is directed to HMG-CoA reductase inhibitors in formulations stabilized by the co-crystallization and/or co-precipitation of the active with a buffering substance. Nothing in claims 1, 12, 13 and 17 of the '507 patent or its specification

would have directed the skilled artisan to the claimed polymorph or formulation. Nothing in claims 1, 12, 13 and 17 of the '507 patent or its specification would have identified the problem with using microcrystalline cellulose and the polymorph of the invention in a tablet formulation or the solution to such problem. This is also true of secondary references Pflaum and Yoshioka, for reasons already discussed above in connection with the obviousness rejection. In view of these arguments, applicants respectfully request the Examiner to reconsider and withdraw the obviousness-type double patenting rejections over claims 1, 12, 13 and 17 of the '507 patent in view of Pflaum and Yoshioka.

CONCLUSION

In view of the above amendment and arguments, applicants respectfully request the Examiner to reconsider and withdraw all outstanding rejections. A Notice of Allowance is respectfully requested. The Examiner is invited to contact the undersigned attorney for applicant for any reason related to the advancement of this case.

In the event that additional fees are necessary in view of this amendment then such fees are hereby authorized to be charged to our Deposit Account No. 01-2300 referencing docket number 029489.00023.

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Respectfully submitted,

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